REMARKS

Claims 37-48 remain pending. Favorable reconsideration is respectfully requested.

As set forth in Claim 37, the present invention relates to a process of lyophilization for the preparation of a piroxicam:β-cyclodextrin inclusion compound in a 1:2.5 molar ratio conducted on a kilogram scale, comprising:

(a) dissolving piroxicam and β-cyclodextrin in the molar ratio of 1 to 2.5 and ammonium hydroxide in water brought to a temperature of at least 60 °C;

(b) pouring the piroxicam and β-cyclodextrin dissolved in water from (a) on temperature-controlled shelves of a freeze-dryer pre-cooled to a temperature of at least -30 °C to lower the temperature of the solution to -10 °C at a cooling rate equal to or higher than 1 °C/min, to produce a frozen solution;

(c) further lowering the temperature of the frozen solution to at least -20 °C; and

(d) drying the frozen solution under vacuum,

where the inclusion reaction is complete with complete amorphization of the inclusion compound and complete conversion of the piroxicam to the zwitter-ionic form.

The rejection of the claims under 35 U.S.C. §103(a) over Chiesi et al. (EP 153998) is respectfully traversed. The cited reference fails to suggest the claimed process.

The Office has based the rejection on hindsight.

The Applicant has fount that *'for ensuring the best performances in terms of dissolution rate [...] the manufacturing process should be able to achieve not only the completeness of the inclusion reaction but also the complete amorphization of the whole product. Moreover, since the dissolution profile is strictly dependent on the intramolecular structure assumed by piroxicam in the inclusion compound, the manufacturing process*

should be able to achieve the complete conversion of piroxicam in the zwitter-ionic form' (paragraph [0015]).

Chiesi et al. are silent about the problem that could be met by passing from a lab scale to a kilogram scale, and there is nothing disclosed therein that would motivate or prompt the skilled artisan to maintain in the solid state the same structure of the inclusion complex in solution, with piroxicam in the zwitter-ionic form by strictly controlling the rate of cooling (paragraph [0039]).

In this respect the Examiner states that, *even if the rate of cooling is different, the rate of cooling should not affect the product formed especially since applicant's lyophilized claimed is the same as Chiesi et al.'s lyophilized product [...].*

The Applicant respectfully disagrees with that conclusion and submits the following data:

20 grams of 1:2.5 piroxicam: β-cyclodextrin obtained according to the method of the present invention, corresponding to about 2.1 grams of piroxicam, were put in a dissolution test apparatus Sotax A76, and then 250 ml of water were introduced. Then, the resulting dispersion was maintained under stirring at 125 r.p.m. After 15 minutes, an aliquot of the solution was withdrawn and filtered. The amount of dissolved piroxicam, measured by UV spectrophotometry, turned out to be 0.5 g/100 ml.

Under similar conditions, using 7.5 grams of 1:2.5 piroxicam: β-cyclodextrin, corresponding to 0.78 grams of piroxicam, the lyophilized product of Chiesi et al. gave rise after 30 minutes to an amount of dissolved piroxicam of 0.0453 g/100 ml (see page 5, lines 15-29).

These data demonstrate that the dissolution kinetics of the lab scale lyophilized product of Chiesi et al. is slower than that of the lyophilized product of the present invention. The data will be submitted in the form of a Declaration shortly.

Page 5, last paragraph

The Applicant respectfully observes that, if the process of Chiesi et al. is carried out on a kilogram scale, crystallization of β-cyclodextrin at 50-55°C occurs and this occurrence does alter the characteristics of the obtained product as residual crystalline β-cyclodextrin will be present and complete amorphization of the whole product will be no longer possible.

Page 6, first paragraph

As it can be appreciated from the website page http://en.wikipedia.org/wiki/Freeze_drying, the skilled artisan knows that, during lyophilization, it is important to cool the material below its eutectic point, which the lowest temperature at which the solid and liquid phases of the material can coexist. In fact, on a phase diagram, this is the temperature below which only the solid phase exists.

When only the solid phase exist, heat can be added to allow frozen water in the material to sublime directly from the solid phase to gas.

Therefore, the temperature achieved below the eutectic point is not critical.

On the contrary, in the case of the lyophilized product of the present invention, the rate of cooling for reaching the temperature of complete freezing (-10°C) as claimed is important in the present invention.

Page 9, paragraph starting with 'After 210 min [...]'

The Examiner argues that *'for this process the cooling rate is less than that disclosed by applicant in the applicant's Declaration'.*

The Applicant respectfully disagrees as the lowering of the temperature does not proceed with the same rate through the whole range.

Again, what it is critical is the rate of cooling for reaching the temperature of complete freezing (-10°C) while the cooling rate, and hence the time for passing from the temperature of -10°C to what of -30°C is not critical, as explained in paragraph [0049] of the specification.

Therefore, the time of 210 minutes in Example 1 refers to the whole time for lowering the temperature of the solution to the temperature of -30°C, but if the shelves are pre-cooled to a temperature of -40°C, the time for reaching the temperature of -10°C would necessarily be of less than 90 minutes, and hence the relevant cooling rate would turn out to be higher than 1°C/min.

Page 9, last paragraph

As reported above, the Applicant has demonstrated that the dissolution kinetics of the lab scale lyophilized product of Chiesi et al. is slower than that of the lyophilized product of the present invention.

It is also the Applicant's belief that the data disclosed in the Scappaticci Declaration clearly demonstrated that, by applying the teaching of Chiesi et al. on a kilogram scale, it is not possible to obtain a lyophilized product with all the characteristics of the lymophilized product of the present invention, as residual crystalline β-cyclodextrin will be present and complete amorphization will be no longer possible.

In view of the foregoing, the claimed process is not obvious over Chiesi et al. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Applicants submit that the present application is in condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

James J. Kelly, Ph.D.
Attorney of Record
Registration No. 41,504

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413 -2220
(OSMMN 08/07)